

Reviewer Report

Title: Compartment and Hub Definitions Tune Metabolic Networks for Metabolomic Interpretations

Version: Original Submission **Date:** 1/8/2019

Reviewer name: Shen Tong

Reviewer Comments to Author:

The reviewer strongly encourages the development and debate for metabolomics data visualization to aid interpretation, as the current resources are simply scarce. The manuscript is technically sound, however, the written presentation needs to be drastically improved. There are redundant descriptions throughout the manuscript which hinder the readers' comprehension. The reviewer regrets to see the redundancy blurs the focus of the paper.

The authors ought to present their work concisely and precisely. The reviewer suggests to simply the structure of the manuscript to enhance clarity, shorten non-essential content e.g. Metabolomics measurement, Table 2, numbers of test studies to present. Eventually, the reviewer suggests the authors to have a peer scholar outside the disciplinary to proofread and to be able to comprehend prior to re-submission.

The structure of the paper could primarily reflect:

- * Define compartment and hub in metabolic network visualization. In DyMetaboNet, what are the main functions to modulate compartment and hub [as key background]
- * Comparison of compartmental vs non-compartmental, with hubs vs without hubs (like figure 2, 3 and 4) [as why]
- * How does DyMetaboNet outperform other existing visualization tools? Quantitatively? [as why]
- * Additional technical functionalities to use DyMetaboNet, such as centralization as in table 3. [as how]

The above are the most important messages to reviewers and readers, therefore should be written with high priority and clarity.

Despite of that,

1) Hubs appear to exert a dominant influence on the data visualization. The reviewer is convinced that excluding "hub" metabolites adds the benefit to enlighten metabolites' relationships in a complex network.

2) Non-compartmental network seems to have smaller impact on simplifying metabolites' relationship compared to hubs. As so, the reviewer is not totally convinced to remove compartmental information merely on the argument that metabolomics measurement is not compartment-specific. Therefore, to leave this function optional to users might be a stronger argument.

2b) Additionally, it is because the measurement is not compartment-specific that providing biochemical compartmental information for specific metabolites could be beneficial. The authors could consider preserving the metabolites that are strongly shown to be compartment-specific from database mining (e.g. cardiolipins in mitochondria).

3) The reviewer is happy to see more computational tools being developed to aid data interpretation.

Could I ask how would the authors plan to maintain and expand DyMetaboNet as entries of metabolites and reactions expand in queried databases?

4) How reproducible the DyMetaboNet outcome is, using the same dataset by different users?

Methods

Are the methods appropriate to the aims of the study, are they well described, and are necessary controls included? Choose an item.

Conclusions

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